Effective treatment of painful bone crises in type I Gaucher's disease with high dose prednisolone

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Abstract

In type I Gaucher's disease, episodes of severe disabling bone pain, the so called bone crises, may be resistant to all analgesics, including narcotics. The demonstration of subperiosteal oedema on magnetic resonance imaging (MRI) led to an attempt to use steroids to relieve the oedema and thereby the pain. On eight occasions, five patients with documented bone crises received conventional dose steroids (20 mg/m²/day) with considerable shortening of the attacks. On six occasions five further patients received high dose methylprednisolone (30 mg/kg intravenously or 1 g/m² orally daily for two days), which was followed by oral prednisone for three to five days on the last four occasions. In this latter group, pain relief was evident within several hours. Three treatments were given on an ambulatory basis. The MRI scan of one of these patients showed no subperiosteal fluid collection five days after high dose steroids had been started, and on subsequent x ray examination, there was no periosteal elevation. This treatment should be considered in cases of Gaucher's disease with bone crises.

(Arch Dis Child 1996;75:218-222)

Keywords: Gaucher's disease, high dose prednisolone, bone crises.

Acute episodes of disabling bone pain—the so called bone crises—associated with swelling, tenderness, and warmth at the involved site, with or without systemic fever, polymorphonuclear leucocytosis, and a raised erythrocyte sedimentation rate, are the hallmark of the severest form of type I Gaucher's disease which occurs in some patients with genotypes N370S/84GG, N370S/1VS2 + 1, and N370S/L444P.¹ Fifty five per cent of our patients with these genotypes have suffered such attacks. These attacks are infrequent in patients who are double heterozygotes for N370S. Nine per cent of such patients in our unit have evidence of bone crises. These bone crises may occur up to several times yearly from childhood and become more unusual after puberty. Imaging studies and histological investigations have shown that the bone crisis is the early manifestation of osteonecrosis.² Patients are often admitted to hospital for days or weeks, and the pain is frequently unrelieved by narcotics.³

Methods

During the period 1993-6, 10 patients presented with one or more episodes of bone pain

(total 18 episodes). Patients who presented with acute onset of severe bone pain underwent clinical examination, routine blood studies, and blood cultures. An immediate technetium-99m methylene diphosphonate (MDP) bone scan was performed. Bone crisis was diagnosed by the demonstration of decreased MDP uptake in the painful area.⁴ If this study was not helpful, magnetic resonance imaging (MRI) was performed, and a high intramedullary and subperiosteal signal on T1 and T2 weighted sequences was considered diagnostic of bone crisis.⁵⁻⁷ Since osteomyelitis can show a similar clinical picture, it is imperative to rule out this condition by the bone scan, which would show increased uptake in this situation.

After acute bone crisis was diagnosed and osteomyelitis ruled out, and since no effective treatment was available apart from analgesics, informed consent was obtained and treatment with steroids was started.

In 14 episodes in 10 patients, there was clear documentation according to the above criteria that a bone crisis had occurred. Initially, conventional doses of prednisone (20 mg/m²/

Figure 1 Technetium-99m methylene diphosphonate bone scan of lower limbs of patient MN, aged 16 years, showing an area of reduced uptake in the upper third of the left tibia (arrow) compatible with the diagnosis of acute bone crisis.

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Accepted 11 May 1996.

Table 1 Prednisone induced pain relief in Gaucher's disease patients

Patient	Age (years)	Date	Site	Prednisone dose (PO)	Pain relief
HN	15	9/90	Proximal tibia	20 mg × 3	8 hours
EM	7	1/91	Tibia	20 mg × 2	'few days'
		10/92	Distal femur	10 mg × 3	4 days
DF	7	4/92	Femoral head	20 mg × 2	2 days
	8	8/93	Proximal tibia/distal femur	20 mg × 2	5 days
AP	22	8/92	Sacroiliac	20 mg × 3	12 hours
		9/92	Talus	20 mg × 3	5 days
GK	11	5/94	Left hand	40 mg × 3	4 days

day) were used in five patients on eight occasions. Subsequently, five patients were treated on six occasions with high dose methylprednisolone, either 30 mg/kg intravenously × two days or 1 g/m² orally × two days. Because of breakthrough pain in the first of the latter patients treated with high dose methylpred-

Figure 2 Magnetic resonance T2 weighted coronal cut of right femur in an untreated patient during a bone crisis (shown for comparison). Subperiosteal fluid with periosteal elevation is seen in addition to a high intramedullary signal at the same level.

Figure 3 Periosteal elevation of femur in the untreated patient.

nisolone, on the last five occasions the high dose treatment was followed by oral prednisone over three to five days. Three treatments were given on an ambulatory basis.

Results

We were encouraged by the considerable improvement in both severity and length of the painful episode with conventional dose steroids, together with a concomitant improvement in warmth, swelling, redness, and function (table 1). For example, one patient (DF), who was pain-free after two days of treatment on one occasion and after five days on another, had been treated for a previous bone crisis with 22 days of oral slow release morphine. This pain relief, usually occurring within days, was obviously only a step in the right direction but it encouraged us to try high dose steroids. The response to high dose methylprednisolone was even more marked, complete pain relief being achieved within hours with this regimen (table

Table 2 High dose prednisolone induced pain relief in Gaucher's disease patients

Patient	Age (years)	Date	Site	Prednisone dose	Pain relief
YH	24	5/94	Femur, neck	30 mg/kg IV $\times$ 2 days	4 hours*
RM	14	5/94	Distal femur	30 mg/kg IV $\times$ 2 days. Prednisone 60 mg, 3 days	24 hours
	14	8/94	Proximal tibia	1 g/m ² PO $\times$ 2 days. Prednisone 60 mg, 3 days	Considerable improvement within 24 hours. No pain after 2 days
MN	16	7/94	Proximal tibia	1 g/m ² PO $\times$ 2 days. Prednisone 60 mg PO reduced to 10 mg over 5 days	7 hours
AM	5	6/95	Proximal femur	1 g/m ² PO $\times$ 2 days. Prednisone 40 mg PO reduced to 20 mg over 3 days	4 hours
OO	13	4/96	Proximal tibia	1 g/m ² PO $\times$ 2 days. Then as above MN	1 hour pain-free. Pain on walking 24 hours

* Pain returned on day 6, readmitted and treated with prednisone 60 mg/day for 10 days (day 10 to day 20), dose tapered to day 23.

2). This effective treatment of the pain was accompanied in several cases by a clear modification of the typical findings on x ray and MRI and will be discussed in detail later.

Discussion

Type I Gaucher's disease may be associated with episodes of acute onset of severe bone pain, the so called bone crisis, which usually

occur in the first two decades of life. The pain may last from a few days to several weeks.²⁻⁴ The severity is attested to by the recognised difficulty in controlling the pain, even with an intensive narcotic programme.⁸

The bone scan initially shows an area of decreased uptake (fig 1), followed by increased activity six weeks later.⁴ The MRI scan shows a high intramedullary and subperiosteal signal on both T1 and T2 weighted sequences, suggesting a subacute haemorrhage or haematoma.^{5,7,9} Changes indicative of reactive oedema (high T2 weighted and normal T1 images) may be visualised in adjacent muscle (fig 2).⁵⁻⁷ These changes could clearly be seen six days after onset of a bone crisis⁷ and partially resolved after two weeks of bed rest and analgesics in another case.⁵ Other investigators reported that at two weeks muscle oedema had resolved but not the periosteal oedema, but by four months and 10 months no periosteal or muscle oedema was seen.⁶ Radiographs performed four to six weeks later show periosteal elevation in the involved area, which may be reactive to the subperiosteal haemorrhage (fig 3).¹⁰ Six months later, osteonecrosis with areas of low and high bone density can be seen at the site of the crisis.³ Pathological fractures may occur two to 12 months after onset of the crisis.¹¹ Total splenectomy may increase the patient's tendency to bone crises,¹² but partial splenectomy has no such effect.¹³

The pathogenesis of bone crisis in type I Gaucher's disease is unclear,¹⁴ but the immediate relief of pain after open bone decompression surgery has led some investigators to suggest that increased intraosseous pressure plays a role.³ In light of the observation on MRI of accumulated subperiosteal fluid during bone crises,⁶ we hypothesised that the subperiosteal fluid could be causing the pain by stretching the periosteum and might be relieved by steroids. In 1965 Yosipovitch *et al* reported immediate pain relief following decompression of periosteum distended by bloodstained fluid in a Gaucher patient mistakenly thought to have osteomyelitis. He also mentioned treatment with steroids, without giving further details of their effect.²

Our hypothesis was supported by the imaging studies performed on patient MN, who was pain-free seven hours after starting treatment. The bone scan (fig 1) revealed the classic findings of acute bone crisis. However, MRI performed five days after treatment was started showed the typical high intramedullary

Figure 4 No periosteal elevation on x ray film of tibia in patient MN eight weeks after treatment.

Figure 5 Magnetic resonance STIR coronal cut of right femur. (A) A hyperintense signal along the proximal femur is seen before treatment was started (arrow). (B) Five days after treatment with prednisolone was started there is marked reduction in the hyperintensity (arrow).

signals on T1 and T2 weighted sequences, but no subperiosteal change; x ray of this area performed eight weeks later showed no periosteal elevation (fig 4).

Subsequently, patient AM had an MRI scan before and five days after the start of treatment with steroids. The subperiosteal fluid (fig 5A) seen initially was considerably reduced after treatment (fig 5B).

Increased microvascular permeability leading to fluid extravasation occurs in several pathophysiological conditions such as inflammation, sepsis, and in the capillary leak syndrome seen after treatment with high doses of interleukin-2 (IL-2).¹⁵ Cytokines, such as tumour necrosis factor (TNF) and interleukin-1 (IL-1), have been implicated in mediating these effects.¹⁶ Since macrophages are a major source of these cytokines, the finding of an increased number of macrophages in the bone marrow in Gaucher's disease—Gaucher's cells—raises the question of whether the subperiosteal oedema in bone crises is a manifestation of a vascular leak resulting from release of TNF and IL-1 from such cells. These cytokines have profound systemic effects, such as leucocytosis and fever,¹⁷ both seen in bone crises, and may mediate local pro-coagulant effects leading to thrombotic

changes¹⁸ that could also be involved in avascular necrosis in the bone crises of Gaucher's disease. In vitro studies have shown that the addition of glucocerebroside to cultured macrophages stimulates the release of IL-1 and lysosomal enzymes.¹⁹

It is possible that the therapeutic effects of the steroids described in this study are related to their ability to inhibit the generation by macrophages of IL-1 and TNF as well as to inhibition of their actions.²⁰

We changed the route of administration of methylprednisolone from intravenous to oral to allow ambulatory treatment and to prevent the possibility of cardiovascular collapse which has been observed when such doses were given over a shorter period than 30 minutes.²¹ This complication has only rarely been reported in general medical journals, but is well recognised in renal transplantation and in other disorders treated with high dose methylprednisolone, with 16 reports since 1976.²¹

High dose methylprednisolone has recently been used successfully in painful bone crisis in sickle cell anaemia.²² We suggest that MRI studies be performed in such patients to determine if a similar pathophysiology is present, as has been suspected for many years.²³ Following our experience we would suggest that high

dose methylprednisolone treatment should be considered in cases of Gaucher's disease with bone crises. Since this is significantly more effective than the lower dose prednisone regime we would recommend 1 g/m^2 orally $\times 2$ days followed by 60 mg/m^2 prednisone orally daily, reduced to 10 mg over five days. We would, however, strongly suggest reserving this treatment for clearly documented significant bone crises (with bone scan and MRI) to prevent inadvertent high dose steroid treatment of septic osteomyelitis. The treatment is not to be undertaken lightly in these patients, who are often osteoporotic from the disease itself, but it is certainly justified as the only effective means to date of controlling intolerable pain in a severe bone crisis. It is as yet unknown whether this treatment will affect the tendency to fracture at the site of bone crisis.

Enzyme replacement therapy has been reported to prevent the progression of symptomatic skeletal disease,²⁴ and bisphosphonates have generally reduced bone crises and fractures in patients of this type.²⁵ Thus it is hoped that bone crises will become obsolete. However, some patients continue—at least initially—to have such episodes while on enzyme replacement therapy,²⁶ so knowledge of a treatment that can render patients pain-free within hours will still be of value in the future for those caring for patients with bone crisis in Gaucher's disease.

Presented in part at the NIH Technology Assessment Conference on Gaucher Disease, Current Issues in Diagnosis and Treatment, February 27–March 1, 1995, NIH Bethesda, Maryland, USA.

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